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GUARDANT HEALTH, INC.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

GUARDANT HEALTH, INC., a Delaware corporation,

Plaintiff,

v.

NATERA, Inc., a Delaware corporation,

Defendant.

Case No. 21-cv-04062-EMC

DECLARATION OF THEREASA RICH, M.S., IN SUPPORT OF PLAINTIFF'S MOTION FOR TEMPORARY RESTRAINING ORDER

Date: June 3, 2021
Time: 1:45 p.m. (Pacific Time)
Courtroom: Zoom Webinar

Complaint Filed: May 27, 2021

I, THEREASA RICH, M.S., declare as follows:

1. I am a Senior Medical Science Liaison at Guardant Health, Inc. ("Guardant"). I make this declaration in support of Guardant's Motion for Temporary Restraining Order. As Guardant's Senior Medical Science Liaison, I have personal knowledge of the facts set forth in this Declaration, and if called to testify as a witness, could and would competently testify to them under oath.

2. I have a Bachelor of Science degree in Biochemistry and Molecular Biology from Pennsylvania State University, and a Master of Science degree in Human Genetics with a focus in Genetic Counseling from the University of Michigan. I am certified by the American Board of Genetic Counseling, and I have more than 15 years of experience working in the field of

oncology diagnostics and clinical research. Prior to joining Guardant in June 2017, I was a Regional Medical Specialist for Myriad Genetics, and a Genetic Counselor for at the University of Texas M.D. Anderson Cancer Center. I have served as a principal investigator or co-investigator on a wide variety of studies involving cancer genetics and circulating tumor DNA (ctDNA) that have led to 45 peer-reviewed publications and 25 abstract presentations at major scientific meetings. A copy of my *curriculum vitae* is provided in **Exhibit A**.

3. My role as a senior medical science liaison with Guardant involves engagement of key opinion leaders regarding the clinical value of Guardant's cell free DNA testing products, the development of strategic research collaborations, contribution to clinical studies and publications, and provision of clinical education and support across multiple departments with regard to clinical care of patients with cancer and understanding of Guardant's products across different use cases in oncology.

4. Guardant offers diagnostic tests to oncologists and other health care professionals across the country to assist in the clinical management of cancer in their patients. Guardant recently launched its Guardant Reveal™ test ("Reveal") for detection of minimal residual dDisease (MRD) in patients with colorectal cancer (CRC). Reveal is a "liquid biopsy" that detects fragments of dying cancer cells in plasma, known as circulating tumor DNA (ctDNA). Using a simple blood draw, Reveal helps doctors identify CRC patients who, after they have received initial treatment for their cancer, continue to have MRD—that is, a small number of CRC cells remaining in the body that cannot be detected with standard diagnostic tests (such as imaging), but can later multiply and cause recurrence of the disease. MRD testing provides more precise estimates of an individual person's risk for CRC recurrence, thus allowing doctors to have more personalized discussions with their patients on the need for additional therapy or monitoring for recurrence.

5. Guardant competes with Natera, Inc. ("Natera") in offering a ctDNA assay for detecting MRD for CRC patients. However, Natera's product, Signatera™, depends on tumor tissue to identify a panel of mutations to track in blood for that patient. Unlike Signatera, Reveal does *not* require tumor-tissue, and instead is the first commercially available plasma-only ctDNA

assay capable of detecting MRD in post-operative patients with CRC without the need for prior sampling and sequencing of tumor tissue, or the time needed to create a new, customized blood tests for each new patient. Reveal provides significant practical advantages over Signatera that are attractive to busy clinicians including a shorter turnaround time to the first MRD test result and a logistically easy test that just involves a simple blood draw.

6. Reveal launched in February of this year. Guardant recently learned that, shortly after Reveal was launched, Natera began an advertising campaign against Reveal. For example, Natera sent emails in March of 2021 to Guardant's current and potential customers, including leading cancer centers like the Mayo Clinic, with the subject line, "Natera's Commitment to MRD Testing." These emails told customers that "there is "concern" about "other laboratories rushing into the clinical MRD market and making potentially misleading claims with no peer-reviewed evidence" that Natera asserted "may be detrimental to patients." While this email does not specify Guardant or Reveal by name, we are the only company—and Reveal is the only ctDNA assay for detecting MRD—that launched in this timeframe. Natera's email attached a slide presentation entitled "Evidence Review: Tumor-informed vs. tumor-naïve MRD." Because Reveal was, and still is, the only "tumor-naïve" (that is, plasma-only) ctDNA assay for detecting MRD in CRC patients available on the market, Natera's email and slide set necessarily refer to Reveal. Natera's presentation also expressly references the data presented by "Parikh, A. et al." (the "Parikh Study")—a study that involved Reveal. A true and correct copy of this email and its attachment are provided as **Exhibit B.**

7. Natera's "Evidence Review" criticizes "tumor-naïve methods," that is, Reveal, as unsupported by "peer-reviewed evidence." This is not true; the interim data from the very study cited by Natera—the Parikh Study—was peer-reviewed as abstract presentations at three prestigious scientific meetings (ASCO 2019, ESMO 2019, and ESMO 2020) prior to publication in the April 29, 2021 issue of the journal Clinical Cancer Research and was available prior to the launch of Reveal and prior to Natera's "Evidence Review" distribution. True and correct copies of the abstract presentations are provided as **Exhibits C-E**.

8. Beyond Natera's false claim that Reveal is not supported by peer-reviewed

evidence, Natera falsely claims in its Evidence Review that "tumor-naïve" testing has "unknown" performance with respect to Negative Predictive Value ("NPV") and hazard ratios for a single test 30 days post-surgery, emphasizing this point with a chart (See Figure 1 below, entitled, "Three time points matter for performance assessment in CRC"). In fact, as shown in Figure 2 below, these data are available in the ASCO 2019 abstract presented by Parikh et al, available well before the dissemination of the Evidence Review.

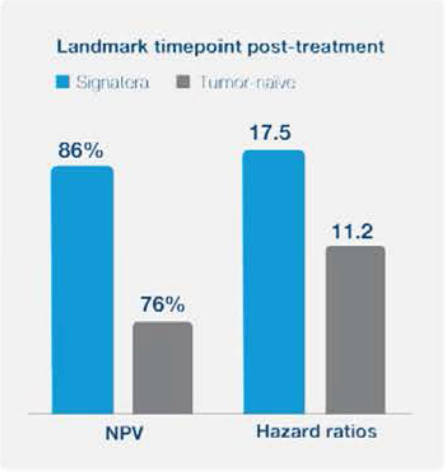
Figure 1. False and Deceptive Comparisons Contained in the Evidence Review

Three time points matter for performance assessment in CRC

	Signatera HR[1,3]	Tumor-naïve HR[2]
Single test 30 days post-surgery	7.2-14.0*	Unknown
Single test post-treatment	17.5	11.2
Serial testing in surveillance	43.5-47.5	Unknown

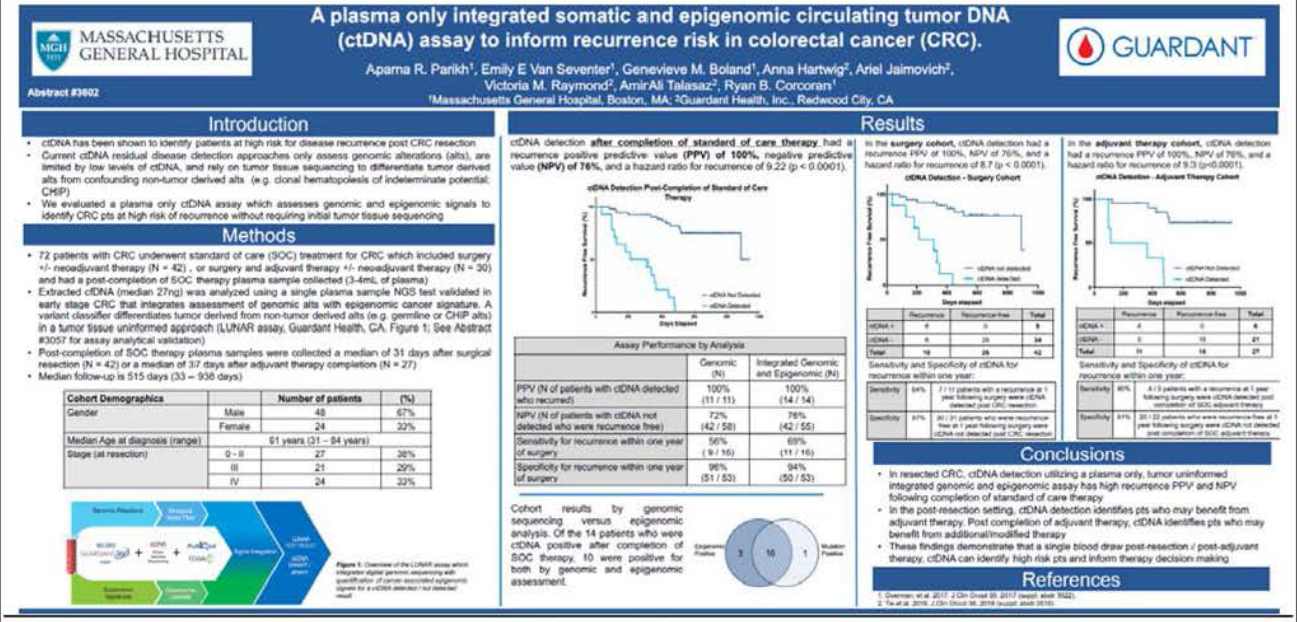
	Signatera NPV[1]	Tumor—naïve[2]
Single test 30 days post-surgery	88% (74/84)	Unknown
Single test post-treatment	86% (44/51)	76% (37/49)
Serial testing in surveillance	97% (58/60)	Unknown

*3/10 post-surgical positive patients cleared ctDNA with adjuvant chemotherapy and did not relapse, implying 70% PPV in patients who receive subsequent ACT



1. Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. JAMA Oncol. 2019;5(8):1124–1131.
2. Parikh, A. et. al. Minimal residual disease (MRD) detection in colorectal cancer (CRC) using a plasma- only integrated genomic and epigenomic circulating tumor DNA (ctDNA) assay. ESMO 2020
3. Tarazona N, Henriksen T, Carbonell-Asins J, et al. Circulating tumor DNA to detect minimal residual disease, response to adjuvant therapy and identify patients at high risk of recurrence in stage I-III CRC. ASCO Poster. 2020

Figure 2. Reveal hazard ratio and NPV data from a single test 30 days post-surgery (presented in 2019 at ASCO)



9. Natera repeats statements disparaging Reveal in two other communications to customers and potential customers including a "white paper to learn how our tumor-informed approach stacks up against a tumor naïve assay" maintained on its website (hereafter referred to as the "white paper") and in its May 2021 "Investor presentation," which was reviewed at its Q1 2021 earnings call and maintained on its website. "Tumor-informed" and "tumor-naïve" assays in the white paper necessarily refer to Signatera and Reveal, respectively, which are the only commercial assays currently available for detecting MRD in CRC patients in the United States. Natera also specifically references the Parikh Study involving Reveal, and a study by Reinert et al. ("Reinert Study") involving Signatera. The performance comparison in the Investor presentation ("Performance Comparison") names Signatera and Reveal explicitly.

10. I have been advised by one of Guardant's medical affairs representatives that shortly after Natera posted the May 2021 performance comparison on its website, Natera also began disseminating it by certified mail (i.e. requiring a signature for receipt)—repeatedly—to at least one of Guardant's customers located in Florida. A member of Guardant's sales team also reports that a Guardant customer in Texas described receiving a chart comparing performance metrics across MRD assays and concluded that since the performance characteristics were put in writing, they must be true.

11. I have personally reviewed Natera's White Paper and Performance Comparison. True and correct copies of this White Paper and Performance Comparison are provided as **Exhibit F** and **Exhibit G.**

12. Before I provide evidence that Natera's claims regarding superior test performance are misleading and unsupported by current evidence, it is worth noting that the majority of the evidence for Reveal's performance is derived from a study *led by* investigators from Massachusetts General Hospital (MGH). MGH is the teaching hospital of Harvard Medical School and was named #6 in the U.S. News & World Report list of "America's Best Hospitals" in 2020. The lead author, Aparna Parikh, MD, is an Assistant Professor of Medicine at Harvard Medical School and is a board-certified medical oncologist with training at prestigious institutions including Indiana University School of Medicine, MGH, and the University of

California San Francisco. She is considered an expert in gastrointestinal cancers and sits on the National Comprehensive Cancer Network (NCCN) guidelines committee for colorectal cancer—a set of guidelines widely used by oncologists in the United States. She is also considered an international expert in liquid biopsies, including in the setting of detecting residual disease after curative intent surgeries. She leads many clinical trials for patients with CRC and has co-authored more than 50 publications.

13. In addition, the study's senior author, Ryan Corcoran, graduated from Princeton University with an AB in Molecular Biology and received an MD and a PhD in Cancer Biology from the Stanford University School of Medicine. He is a board-certified medical oncologist, Associate Professor at Harvard Medical School, the director of MGH's Gastrointestinal Cancer Center Program, and Principal Investigator of a translational research laboratory focused on personalized cancer medicine. Dr. Corcoran is widely seen as an expert in gastrointestinal cancers and liquid biopsies, has co-authored more than six dozen publications including the NCI Colon and Rectal-Anal Task Force's whitepaper on ctDNA applications and integration in colorectal cancer. I note he has received consulting fees for his expertise from both Guardant and Natera. Furthermore, the study was co-authored by more than 30 other investigators at MGH who were involved in the preparation and review of all of the data and analyses included in the Clinical Cancer Research publication.

14. The design and implementation of the Parikh Study—including timing of sample collection and decisions around data analyses—*were led by a team of prestigious and experienced investigators at MGH and not by Guardant Health.* In fact, MGH issued a press release in April of 2021 underscoring MGH's leading role in the publication of the first ever data from a tumor-uninformed test for MRD (**Exhibit H**). Guardant did not provide financial support for the Parikh Study. Guardant's only contributions to the study was that it analyzed patient plasma samples without charge and provided feedback on the data analysis and manuscript preparation, which MGH was not contractually obligated to incorporate.

15. In the following paragraphs, I have outlined why Natera's supposed quantitative demonstration that Signatera is superior to Reveal, presented as facts in its Evidence Review,

white paper, and Performance Comparison is unfair, false and deceptive.

16. To begin with, it is a fundamental principle that any valid comparison between diagnostic tests, including ctDNA assays for detecting MRD in CRC patients, must be supported by properly designed studies that directly compare the two assays using the same test procedures and protocols and in a comparable patient population. *See* Irwig et al., "Designing studies to ensure that estimates of test accuracy are transferable." *BMJ* 2002 Mar. 16; 324(7338): 669-71. Cross-test comparisons, especially where the purpose and methodology of the underlying studies differ significantly, and/or where the studies are conducted in different patient populations, necessarily lead to a misleading apples-to-oranges result that cannot legitimately be used to claim that one test is superior to the other. Indeed, Natera recognizes that "direct comparisons are challenging" in the Conclusions section of its white paper, yet promotes these direct comparisons as evidence that Signatera is superior to Reveal anyway.

17. Natera's "performance comparisons" are not based on a study directly comparing Signatera and Reveal; instead Natera inappropriately cherry-picks data from the Reinert Study concerning Signatera and the Parikh Study concerning Reveal. True and correct copies of the published versions of the Reinert and Parikh Studies are attached as **Exhibit I** and **Exhibit J**.

18. I have personally reviewed both the Reinert and Parikh Studies and the data on which they rely. The Reinert and Parikh Studies used very different sample collection strategies and analysis methods, and examined patient populations with different CRC recurrence risk profiles. Using data from these two very different studies to compare and contrast Signatera and Reveal is fundamentally flawed and yields unreliable results.

19. Natera's comparative metrics include "pre-surgical sensitivity," "failure rate," "diagnostic lead time," "post-surgical" and "serial longitudinal" negative predictive value (NPV), and Hazard Ratio, among other categories (see Figures 1, 3, and 4). Natera also claims superior performance from metrics unrelated to an assay's performance, such as number of patients analyzed, number of blood tubes required, and quantitation of ctDNA burden.

Figure 3. False and Deceptive Comparisons Contained in the White Paper

Table 3. *Comparison of hazard ratios and negative predictive values of tumor-informed and tumor-naive assays in early-stage CRC*

	Signatera (tumor-informed assay)[4,7,8]	Tumor-naive assay[19]
Hazard ratios of ctDNA (positive vs negative)		
Post-surgery (30 day single test)	7.2-14.0*	Not Validated
Post-ACT (single test)	17.5	9.8-11.2**
Serial testing	43.5-47.5	11.4
Negative predictive value (NPV)		
Post-surgery (30 day single test)	88% (74/84)	Not Validated
Post-ACT (single test)	86% (44/51)	76% (37/49)**
Serial testing	97% (58/60)	82% (41/50)

Figure 4. False and Deceptive Comparisons Contained in the Performance Comparison

Signatera vs. Reveal performance comparison

	Signatera	Reveal
Validation data published or presented (# patients analyzed)	> 2,000[1,2]	< 150[4,5]
Pre-surgical sensitivity in CRC	89-94%[1,3]	47%*[4]
Failure rate in CRC – tissue and plasma combined	< 3%[3]	12-14%[4]
Number of blood tubes required	2	4
Diagnostic lead time vs. radiographic recurrence in CRC (avg)	8.7 months[1]	~4 months*[4]
Post-surgical NPV/PPV in CRC (30 days post-surgery)	88% / 100%**[1]	not reported[4]
Serial longitudinal NPV in CRC	97%[1]	82%[4]
Serial longitudinal Hazard Ratio in CRC	43.5[1]	11.4[4]
Serial longitudinal sensitivity in CRC	88-94%[1,2]	69%[4]
Quantitation of ctDNA burden for monitoring purposes	Tumor copies per mL	none

20. While Natera claims that the number of "patients analyzed" in "published or presented studies," is more than two thousand for Signatera, those numbers do not prove the superiority of the clinical performance of one ctDNA assay over another. Moreover, the ">2,000" number reported for Signatera appears to be inflated. It appears that Natera is double-counting some patients whose data were used in more than one published study. The number also appears to include patient populations presenting with cancers other than CRC for which Reveal is neither

validated nor currently intended to be used (see Page 4 of the Evidence Review at Exhibit B).

21. Natera's claim that Signatera requires only two "blood tubes," while Reveal requires four is also not a "performance" metric. Moreover, Natera's assertion that Reveal "requires" 4 tubes of blood is untrue. Reveal, like Signatera, only requires 2 tubes of blood. Guardant's Reveal kit collects 2 additional tubes of blood to provide redundancy in the rare event of an assay failure on the first 2 blood tubes; thereby protecting patients from having to provide another blood sample and saving valuable time.

22. "Quantitation of ctDNA for monitoring purposes" is an assay feature, not an appropriate measure of assay performance. Natera's assertions that quantitation, i.e., "quantitative results," is necessary to achieve good assay performance, or is an "MRD assay requirement," is at least misleading, in light of the intended use of both the Signatera and Reveal assays, i.e., to identify CRC patients at increased risk for recurrence of the disease. All available evidence I have reviewed shows that the presence of ctDNA-regardless of the quantity-indicates a high likelihood of recurrence. As such, the clinical utility of ctDNA quantitation in the context of the intended use of the assay is unclear. Signatera's practice of reporting a "mean tumor molecules per mL" value, and Reveal's choice not to do so, does not represent a performance advantage for one over the other.

23. Natera's comparison of "failure rate in CRC," and its claim of Signatera's superiority over Reveal, are false. The Parikh study which Natera cites as proof that Reveal has a "12-14%" failure rate (vs. a "< 3%" rate for Signatera) relied on banked plasma or cell free DNA samples that had input amounts substantially less than recommended. In fact, the Parikh Study reports, "the extracted ctDNA quantity or quality was below the recommended and optimal input levels for the assay" and "may have affected overall performance characteristics." In point of fact, Guardant's data shows that the actual failure rate of Reveal in patient care testing is less than 1%, better than Signatera's claimed failure rate of less than 3%.

24. Reveal's less than 1% failure rate is derived from actual laboratory analyses of submitted patient blood samples processed in the Guardant laboratories running the assay that clinicians ordered. The derivation of Natera's claimed failure rate appears to be interim data from

the Circulate-IDEA Japan study that will be presented at an upcoming conference (see page 11 of the Investor presentation at Exhibit G). 'The oncology community understands "failure" to mean those instances where a submitted sample produced no result. In my experience, however, the rate of sample failure among submitted tissue samples in the United States is far higher than 3%.

25. The Evidence Review, White Paper, and Performance Comparison all purport to show that the hazard ratios and negative predictive values (NPV) of Reveal are inferior to those of Signatera in early-stage CRC. Here, a "hazard ratio" refers to a comparison between the recurrence rate over time in CRC patients who tested positive for MRD by ctDNA assay, to the recurrence rate in CRC patients who tested negative for MRD by ctDNA. A larger hazard ratio—such as the one reported by Natera for Signatera in the White Paper—suggests that the assay is potentially more useful in successfully distinguishing CRC patients whose cancers will or will not recur. "NPV" refers to the assay's ability to correctly predict which patients will subsequently not develop a recurrence of CRC (i.e., a "negative" test result means CRC will not recur), and a higher percentage NPV is more desirable.

26. Assays of equal sensitivity (ability to correctly identify true positives) and specificity (ability to correctly identify true negatives) yield dramatically different NPVs and hazard ratios when applied to patient populations with different recurrence risk profiles. This can be demonstrated mathematically. Let's suppose, for example, that we have a test for COVID-19 that has a diagnostic test sensitivity of 40% (correctly identifies COVID-19 in 40% of patients truly affected with the disease) and specificity of 100% (correctly identifies the absence of COVID-19 in all cases). Let's then calculate this test's NPV in two different hypothetical populations with different risk profiles: 100 patients in a hospital with a confirmed diagnosis of disease and 100 asymptomatic people from a remote island that did not allow travel after the start of COVID-19 and has zero confirmed cases. In the hospital population, the NPV for the test is 0% since no patients with a negative test are unaffected with COVID-19 (calculated as 0/60 from the 60 patients the test would have falsely identified a negative). In the island population, the NPV for the test is 100% since all patients are unaffected with COVID-19. In other words, NPV provides a probability that one does not have a disease based on the results of a given test. While

it is a measure of the accuracy of the test, it is strongly influenced by the prevalence of the disease in the population studied. The Reinert Study examined patients in Denmark, with stages I to III CRC, where the disease prevalence (i.e. CRC recurrence rate) was 19% (24/125 evaluable patients). In contrast, the population in the Parikh Study comprised patients with stages I-IV CRC and those patients had more than twice the disease prevalence (recurrence rate of 39%, 27/70 evaluable patients) than those included in the Reinert Study. *As such, NPV cannot be used as "'proof'" that Signatera has better performance than Reveal.* Hazard ratio calculations are more complex than NPV calculations, but are similarly heavily influenced by the underlying disease prevalence (i.e. recurrence risk). Furthermore, the survival analyses used to derive the hazard ratios in the Parikh and Reinert studies used different methodologies; similarly *hazard ratio differences cannot be used as "'proof"' that Signatera has better performance than Reveal.*

27. Natera further criticizes Guardant for not providing hazard ratio and NPV data for the 30-day post-surgery timepoint and claims that "MRD status 30 days after surgery but before chemotherapy [is] required to assess the expected performance." Contrary to Natera's claims, such data are available in the supplemental section of Parikh's Clinical Cancer Research publication and were previously reported in an interim analysis of the same data at ASCO 2019. But while the data in fact are available, the Parikh Study investigators chose to focus on data from samples collected at a "landmark" timepoint approximately 30 days *after all definitive initial treatment*. This landmark was chosen because for many CRC patients, surgery to remove the tumor does not represent the end of the patient's initial treatment regimen; many patients receive adjuvant chemotherapy. In fact, nearly 55% of the participants in the Parikh Study received additional treatment post-surgery.

28. Examining performance metrics like NPV and hazard ratio based on data from samples collected after surgery, but before adjuvant chemotherapy, are descriptive, but make it hard to interpret and compare actually assay performance. In short, these measures are confounded by the effect of the subsequent chemotherapy—one cannot sort out the accuracy of the assay from the effects of the chemotherapy. Adjuvant chemotherapy kills CRC cells in some patients. Thus, a patient that has MRD after surgery (before adjuvant chemotherapy) but has a

negative assay result (i.e. a false negative) may thereafter be rid of the MRD by the chemotherapy. In that circumstance, the NPV for the assay would be artificially inflated, not because the assay had superior performance, but because chemotherapy *works to lower the risk of disease and therefore works to improve the NPV*. In the Reinert Study, 52 of the 94 (55%) patients included in the postoperative day 30 analysis were reported to have received adjuvant chemotherapy.

29. Other assay performance metrics, such as sensitivity to detect recurrence, are not subject to the confounding effect of post-operative chemotherapy. However, Natera chose not to report this important and likely more relevant metric in its marketing materials. The data reported by the Reinert Study shows that Signatera's sensitivity to detect recurrence at the 30-day post-surgical timepoint is 41% (7/17 patients). The supplemental data reported by the Parikh Study show Reveal has a sensitivity to detect recurrence at a similar timepoint of 54% (14/26 patients). Moreover, looking only at the subset of the Parikh Study's patients with stage I-III disease (excluding stage IV patients), i.e., a more similar stage representation to the patient group examined by Reinert, Reveal still shows a higher sensitivity for recurrence of 56% (9/16 patients). Advertising that Signatera has better performance while leaving out clinically meaningful assay sensitivity data that suggests better performance for Reveal is inherently misleading.

30. Natera's claims of Signatera's superior "pre-surgical sensitivity" ("89-94%" vs. "47%") is highly misleading. Neither Reveal nor Signatera is intended to be used as a diagnostic tool pre-surgery, and as an assay that relies on the existence of surgically-excised tumor tissue, Signatera cannot be used as a pre-surgical diagnostic tool. The Parikh Study that Natera cites as the source for this statistic examined a patient cohort where nearly half (45%) of the group had received chemotherapy prior to surgery and in which the pre-surgical sample volumes were far lower than recommended (all samples had <4mL of plasma rather than the recommended 8-10mL). Sensitivity of MRD assays is linked to sample volume, and lower sample volume necessarily lowers the ctDNA detection rate. Indeed, Parikh et al specifically point out that "our plasma input volumes…may have affected overall performance characteristics." Guardant's

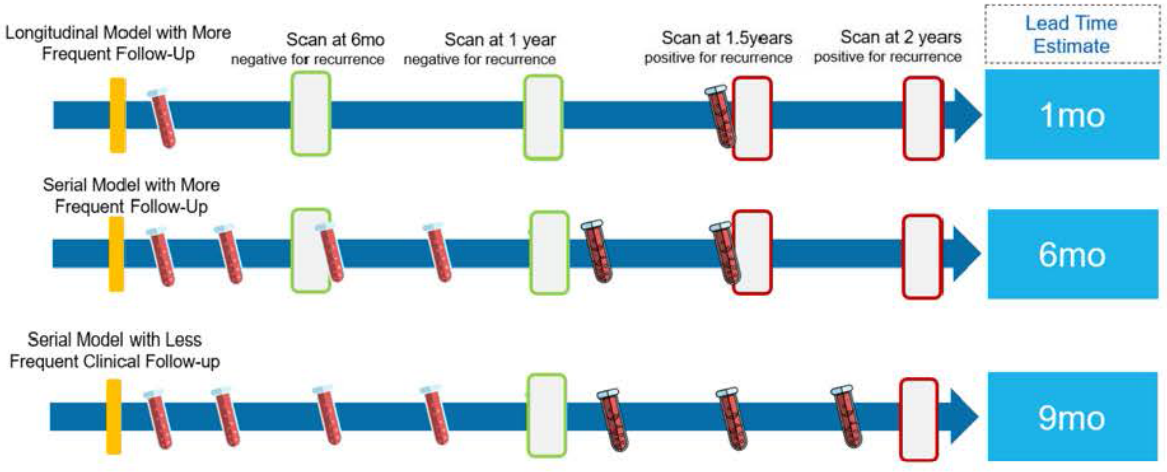
internal data shows that in samples with appropriate volume collected in patients who have not received neoadjuvant chemotherapy, the pre-operative sensitivity of Reveal is >80% in patients with early-stage CRC.

31. Natera's comparisons of the "serial longitudinal" NPV, hazard ratio, and sensitivity of Signatera and Reveal are also misleading. It is critically important to understand the definitions of "serial" and "longitudinal" as defined in the Parikh and Reinert Studies. The Reinert Study collected samples 30 days after surgery, after adjuvant chemotherapy, and "serially" every 3 months for up to 3 years. Serial testing is relevant for recurrence detection because is clear from multiple published studies that samples collected closer to the time of a patient's recurrence have higher sensitivity than samples collected well before the time of the recurrence. The sample collection strategy in the Parikh Study was drastically different. The study focused on patients who had blood samples collected 30 days after all definitive treatment (landmark timepoint). A subset of these patients happened to have a sample collected at the 30 day post-surgical timepoint (similar to the Reinert Study), and a subset of their cohort happened to have at least one additional sample collected after the landmark timepoint (but in no way similar to the "serial" sample collection described in the Reinert Study). The Parikh Study of Reveal was therefore not designed to provide "serial" test data (i.e. data at regular time intervals after the initial test), and consequently the Parikh Study did not report "serial longitudinal" NPV, specificity, or hazard ratio. Natera biased its comparison in Signatera's favor by reporting Reveal's "longitudinal" sensitivity of 69% in comparison to Signatera's "serial" sensitivity of 88-94%. Reveal's longitudinal sensitivity was calculated using data from the subset of patients who had at least one blood draw after the landmark timepoint and is clearly described in the methods of the paper. The timing of this additional draw was highly variable relative to the time of recurrence, and is not comparable to the timing of serial samples collected by the Reinert Study (i.e., every three months). Consequently, this is a fundamentally misleading apples-to-oranges comparison.

32. Moreover and notably, the Parikh Study did include a subset of 22 patients who had both a CRC recurrence and a Reveal blood sample taken within 4 months of recurrence.

Parikh and her colleagues used this subset of patients to estimate what the serial sensitivity of Reveal would be if samples had been collected every 3 months, using the premise that if samples were collected every 3 months, then there would have been a sample collected within 3-4 months of recurrence detection. This is a logical and reasonable method to estimate the "serial" sensitivity parameter. If the data from this subset are used"", Reveal has an estimated sensitivity of 91%; a sensitivity that is at least comparable to Signatera's serial sensitivity estimate. Natera does not report this statistic in its performance comparison, despite it being clearly outlined in the Parikh Study, however, and instead chose to report the highly misleading hybrid "serial longitudinal" metric.

33. Natera's unfavorable comparison of Reveal's "diagnostic lead time vs. radiographic recurrence," to that of Signatera, is also false and misleading. The determination of a "diagnostic lead time estimate" is affected as much by the frequency of the tests used to derive the estimate as by the assay's sensitivity. As the following graphic shows, the diagnostic lead time estimate for the same assay and the same patient with the same test results can vary significantly, depending on how often follow-up tests (blood assay ***and*** radiographic scans) are conducted. A diagnostic lead time estimate that is based on frequent ctDNA testing and less frequent radiographic imaging will provide longer lead times compared to strategies where ctDNA testing is less frequent and strategies where radiographic imaging is more frequent.



34. The "diagnostic lead time estimate" for Signatera was developed from data reported by Reinert. As above the Reinert Study protocol called for CRC patients to undergo

ctDNA testing 30 days after surgery, after adjuvant chemotherapy, and every three months afterwards (a frequent ctDNA testing strategy). The Reinert Study was also conducted in Denmark, where radiographic scans are relatively infrequent. Abstracts authored by Reinert and colleagues using Signatera as the ctDNA testing platform reported that radiographic scans were performed 12 months and 36 months after surgery.

35. In contrast, the Parikh Study was performed in the U.S. where the frequency of radiographic imaging is more variable on a per-patient basis, but also tends to occur more often (typically every 6-12 months after surgery as recommended in the NCCN guidelines). The typical practice at MGH is to follow NCCN guidelines, and some patients may be recommended to have imaging even sooner, every 3 months (personal communication with Dr. Parikh). In addition, the Parikh Study did not involve patient ctDNA testing at regular intervals over a specified period of time and was not designed to estimate "diagnostic lead time." Consequently, the Parikh Study did not report an estimated diagnostic lead time for Reveal, and the "~ 4 month" value Natera reports in its comparison chart is not based on any calculation provided by the authors of the study. Given the difference in typical radiographic imaging practices between Denmark and the United States, it is likely that any diagnostic lead time estimates would be longer in a study in Denmark, even if sample collection protocols were the same and assay performance was identical.

36. Natera's white paper further asserts that: "Without the genomic information for each primary tumor, tumor naïve assays are unable to filter out background biological noise from CHIP or to avoid tracking driver mutations that may be subjected to selection pressure from treatment . . . ." This assertion is false. Reveal can and does filter out biological noise sources such as mutations caused by clonal hematopoiesis ("CHIP") bioinformatically. In fact, data Guardant publicly presented in 2018 on a prototype of the Reveal assay showed 100% specificity with incorporation of the CHIP filter. A true and correct copy of this presentation is provided as **Exhibit K**. Furthermore, the three abstract presentations provided at Exhibits C-E clearly describe that Reveal (at the time known as its LUNAR or LUNAR-1 assay) contains a variant filter that differentiates tumor derived from non-tumor derived genomic alterations (e.g. CHIP alterations) as does the publication by Parikh in Clinical Cancer Research.

37. I have provided a technical review explaining why Natera's supposed quantitative demonstration that Signatera is superior to Reveal is unfair, false and deceptive. I believe that Guardant has presented a true and accurate depiction of Reveal's performance based on available data, and that its performance is competitive and warrants a space in the MRD testing market. The data and methods used to calculate Reveal's performance were analyzed and prepared by independent collaborators at MGH, peer-reviewed, recommended for publication, and ultimately accepted for publication by the editors at Clinical Cancer Research, providing further validation of the scientific merit behind Reveal's performance claims. Reveal is also being used in three prospective interventional trials (including one lead by Dr. Parikh) and I personally have been approached on multiple occasions by investigators with expertise in ctDNA and clinical research who are interested in using Reveal for their clinical trials (thus providing further evidence that there is interest and demand for an assay with Reveal's performance).I have written this declaration in support of Guardant because I believe Natera's false and misleading claims are harmful to Guardant, but more importantly are detrimental to patient access to MRD testing and could hinder progress in identifying better treatment strategies for patients with CRC. Current standard of care is failing too many patients with CRC and MRD testing is poised as one of the most promising strategies to revolutionize their management and improve their outcomes. Guardant is committed to being part of the solution and attempts by Natera to discredit Reveal's performance are harmful to these efforts.

38. Guardant has learned that Natera plans a 40 minute presentation concerning Signatera during the 2021 American Society of Clinical Oncology (ASCO) meeting, on June 7, 2021. Natera states that this presentation entitled, "The value of a tumor-informed approach for early MRD detection," will help attendees "[l]earn why a tumor-informed approach using Signatera enables the highest level of sensitivity and specificity required to stratify high risk patients and accurately detect molecular residual disease (MRD)."(emphasis added). A true and correct copy of Natera's advertisement for its ASCO presentation is provided as **Exhibit L**.

39. Given the comparative language in this description, it seems clear that Natera plans to compare and contrast Signatera against Reveal. The annual ASCO meeting is one of the

world's premier educational and networking conferences for oncology professionals who care for people living with cancer. In 2020, the annual ASCO conference attracted more than 40,000 oncology professionals from 138 countries, to learn about new clinical cancer advances in every area of cancer research. The content presented at this meeting—which like the 2021 meeting, was presented virtually—included nearly 5,300 abstracts and more than 2,300 oral and poster presentations, highlight sessions and clinical symposia, that together have been viewed more than 2.5 million times. Given that MRD testing is an exciting 'hot topic' in oncology, we have reason to believe that Natera's ASCO presentation may be well attended, including by current and potential future Guardant customers and collaborators, and that any further repetition of the false and misleading claims Natera has alleged about the performance of Reveal may cause irreparable damage to Guardant's brand and reputation. Importantly, Natera's actions could lead clinicians to not order Reveal for patients who may benefit from MRD testing, including the substantial subset of patients who do not have sufficient tissue for a tissue-informed assay and would have no other option to access MRD testing than Reveal, and could lead investigators to not consider Reveal (and thus have less access to MRD testing) to support clinical trials that could revolutionize the care of patients with CRC.

Pursuant to 28 U.S.C. § 1746, I, Thereasa Rich, certify under penalty of perjury that the foregoing is true and correct. Executed on this 2nd day of June, 2021.

DocuSigned by:
Thereasa Rich
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Thereasa Rich, M.S.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

GUARDANT HEALTH, INC.,
a Delaware corporation,

Plaintiff,

v.

NATERA, Inc.,
a Delaware corporation,

Defendant.

Case No. 4:21-cv-04062-EMC

DECLARATION OF THEREASA RICH, M.S. IN SUPPORT OF PLAINTIFF'S MOTION FOR TEMPORARY RESTRAINING ORDER

APPENDIX OF EXHIBITS

Exhibit Description	**Ex. No.**
Parikh et al., Abstract Presentation: Minimal residual disease (MRD) detection in colorectal cancer (CRC) using a plasma-only integrated genomic epigenomic circulating tumor DNA (ctDNA) assay (2020)	E
Natera "White Paper": A comparison of tumor-informed and tumor-naïve approaches for early-state molecular residual disease (MRD) detection (2021)	F
Natera, Inc. Investor Presentation, May 2021 Q1 2021 earnings call	G
Massachusetts General Hospital Press Release "New test detects residual cancer DNA in the blood without relying on tumor data", dated April 30, 2021	H
Reinert et al., Analysis of Plasma Cell-Free DNA by Ultradeep Sequencing in Patients with Stages I to III Colorectal Cancer, JAMA Oncol. 2019;5(8):1124-1131. doi:10.1001/jamaoncol.2019.0528	I
Parikh et al., Minimal Residual Disease Detection using a Plasma-Only Circulating Tumor DNA Assay in Colorectal Patients, Clin Cancer Res Published OnlineFirst April 29, 2021	J
Overman, et al., Abstract Presentation #12044: A *priori* filtering of post-operative circulating tumor DNA predicts recurrence in post-metastaectomy colorectal cancer patients without knowledge of tumor genotype	K
Natera Ad for ASCO Annual Meeting June 7, 2021	L